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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09 462,846	01 13 2000	DAVID A. ESTELL	GC381-US	5580

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EXAMINER

STEADMAN, DAVID J

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 01 22 2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/462,846

Applicant(s)

ESTELL, DAVID A.

Examiner

David J. Steadman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 2,3 and 10-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1,4-9 and 13-17 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: ____

DETAILED ACTION***Status of the Application***

The request filed on 12/04/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/462,846 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1-17 are pending in the application.

Applicants' election without traverse of Group I, claims 1, 4-9, and 13-17, drawn to a microorganism having a mutation or deletion of the gene encoding cysteine protease-1 (CP1) and methods for the production of a heterologous protein using said microorganism in Paper No. 9, filed 04/25/01 is acknowledged.

Claims 2, 3, and 10-12 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Drawings

1. The drawings submitted with this application have not been reviewed by a draftsman at this time. Upon allowance of the claims, the draftsman will perform a review. Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

Specification/Informalities

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Bacillus Subtilis with Inactivated Cysteine Protease-1". See MPEP § 606.01.

Claim Objections

3. Claims 4 and 6-8 are objected to because they depend on non-elected claims 2 and 3.

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4. Claims 13 and 16 are objected to as being drawn to non-elected subject matter.
5. Claims 1 and 15-17 are objected to because of the recitation of "CP1" in claims 1 and 16 and "apr", "npr", "epr", "wpr", and "mrp" in claims 15 and 17. Abbreviations, unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.
6. Claims 1, 7, 9, and 16 are objected to because of the following informalities: the terms "encoding CP1 said mutation" in claim 1, "consisting of hormone, enzyme, growth factor and cytokine" in claim 7, "consisting of a proteases" in claim 9, and "having at mutation" in claim 16 are grammatically incorrect and should be replaced with, for example, "encoding CP1, said mutation", "consisting of a hormone, an enzyme, a growth factor and a cytokine", "consisting of proteases", and "having a mutation", respectively. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 5 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
8. Claim 5 is confusing in the recitation of "B. subtilis... ..B. lautus and Bacillus thuringiensis". It is suggested that applicants maintain consistency in the claim by, for example, reciting either "Bacillus subtilis... ..Bacillus lautus and Bacillus thuringiensis" or "B. subtilis... ..B. lautus and B. thuringiensis".
9. Regarding claim 9, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).
10. The term "selected from the group consisting of: a proteases, carbohydrases, and lipases; isomerases such as racemases, epimerases, tautomerases, or mutases; transferases, kinases and phosphatases" in claim 9 is confusing. It is suggested that the language be replaced with, for example,

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"selected from the group consisting of: proteases, carbohydrases, lipases, isomerases, epimerases, tautomerases, mutases, transferases, kinases, and phosphatases."

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 4-9, and 13-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4-9, and 13-17 are rejected because the claims recite a genus of gram-positive microorganisms (claim 1), a genus of Bacilli (claim 4), or the Bacilli species listed in claim 5 having a genus of mutations or a deletion of a genus of genes encoding CP1 resulting in the inactivation of CP1 proteolytic activity, a genus of gram-positive microorganisms having a mutation or deletion of a genus of genes encoding CP1 (claim 16), and optionally having a genus of mutations or a deletion in at least one of a genus of genes encoding apr, npr, epr, wpr, and mrp (claim 17), or a method of producing a heterologous protein using a genus of Bacilli (claim 13) or Bacilli species of claim 14 having a genus of mutations or a deletion in a genus of genes encoding CP1 and, optionally comprising a genus of mutations or a deletion in at least one of a genus of genes encoding apr, npr, epr, wpr, and mrp (claim 15). The specification teaches only one representative species of such microorganisms or *Bacillus* host cells, namely, *Bacillus subtilis* with a deletion in the polynucleotide of SEQ ID NO:1, resulting in the inactivation of CP1 proteolytic activity. The specification fails to disclose any other microorganisms by any identifying structural characteristics or properties other than the functionality of having a mutation or deletion of part or all of the gene encoding CP1 resulting in the inactivation of the CP1 proteolytic activity

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or the functionality of having a mutation or deletion of part or all of the gene encoding CP1. Given the lack of description of additional representative species of microorganisms as encompassed by the genus of the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

12. Claims 1, 4-9, and 13-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Bacillus subtilis* host cell with a deletion of the polynucleotide of SEQ ID NO:1, thereby resulting in the inactivation of CP1 proteolytic activity and a method for producing heterologous proteins using said host cell, does not reasonably provide enablement for *any* gram-positive microorganism (claim 1), *any* *Bacillus* (claim 4), or *any* of the *Bacilli* listed in claim 5 having *any* mutation or deletion of *any* gene encoding CP1 resulting in the inactivation of CP1 proteolytic activity, *any* gram-positive microorganism having *any* mutation or deletion of *any* gene encoding CP1 (claim 16), and optionally having *any* mutation or deletion in *any* of the genes encoding *apr*, *npr*, *epr*, *wpr*, and *mrp* (claim 17), or a method of producing a heterologous protein using *any* *Bacillus* (claim 13) or *any* *Bacilli* of claim 14 having *any* mutation or deletion in a gene encoding *any* CP1 and, optionally comprising *any* mutation or deletion in *any* of the genes encoding *apr*, *npr*, *epr*, *wpr*, and *mrp* (claim 15). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 4-9, and 13-17 are so broad as to encompass *any* gram-positive microorganism, *any* *Bacillus*, or *any* of the *Bacilli* listed in claim 5 having *any* mutation or deletion of *any* gene encoding CP1 resulting in the inactivation of CP1 proteolytic activity, *any* gram-positive microorganism having *any* mutation or deletion of *any* gene encoding CP1, and optionally having *any* mutation or deletion in *any* of the genes encoding *apr*, *npr*, *epr*, *wpr*, and *mrp*, or a method of producing a heterologous protein using *any* *Bacillus* or *any* *Bacilli* of claim 14 having *any* mutation or deletion in a gene encoding *any* CP1 and, optionally comprising *any* mutation or deletion in *any* of the genes encoding *apr*, *npr*, *epr*, *wpr*, and *mrp*. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard

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to the extremely large number of gram-positive microorganisms or Bacilli having mutations or deletions of the genes encoding CP1, apr, npr, epr, wpr, and mrp as encompassed by the claims. Since the amino acid sequence of an encoded protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a *Bacillus subtilis* host cell with a deletion of the polynucleotide of SEQ ID NO:1, thereby resulting in the inactivation of CP1 proteolytic activity and a method for producing heterologous proteins using said host cell.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass *any* gram-positive microorganism, *any* *Bacillus*, or *any* of the Bacilli listed in claim 5 having *any* mutation or deletion of *any* gene encoding CP1 resulting in the inactivation of CP1 proteolytic activity, *any* gram-positive microorganism having *any* mutation or deletion of *any* gene encoding CP1, and optionally having *any* mutation or deletion in *any* of the genes encoding apr, npr, epr, wpr, and mrp, or a method of producing a heterologous protein using *any* *Bacillus* or any Bacilli of claim 14 having *any* mutation or deletion in a gene encoding *any* CP1 and, optionally comprising *any* mutation or deletion in *any* of the genes encoding apr, npr, epr, wpr, and mrp because the specification does not establish: (A) the sequences of CP1 polypeptides or encoding polynucleotides of *any* gram positive microorganisms or *any* Bacilli or methods

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of isolating said sequences that would enable one of skill in the art to delete CP1 from *any* gram positive microorganisms or *any* Bacilli to delete the gene encoding CP1; (B) regions of CP1 from *any* gram-positive microorganism, *any* Bacillus, or *any* of the Bacilli listed in claim 5 that may be mutated with an expectation of obtaining the desired biological activity; (C) regions of CP1 from *any* gram-positive microorganism or *any* Bacillus apr, npr, epr, wpr, and mrp that may be mutated with an expectation of obtaining the desired biological activity; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including *any* gram-positive microorganism, *any* Bacillus, or *any* of the Bacilli listed in claim 5 having *any* mutation or deletion of *any* gene encoding CP1 resulting in the inactivation of CP1 proteolytic activity, *any* gram-positive microorganism having *any* mutation or deletion of *any* gene encoding CP1, and optionally having *any* mutation or deletion in *any* of the genes encoding apr, npr, epr, wpr, and mrp, or a method of producing a heterologous protein using *any* Bacillus or any Bacilli of claim 14 having *any* mutation or deletion in a gene encoding *any* CP1 and, optionally comprising *any* mutation or deletion in *any* of the genes encoding apr, npr, epr, wpr, and mrp. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 4-9, and 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 89/10976. Claims 1, 4-9, and 13-17 are drawn to a gram-positive microorganism, *Bacillus*, or the *Bacilli* species listed in claim 5 having a mutation or deletion of a gene encoding CP1 resulting in the inactivation of CP1 proteolytic activity, a gram-positive microorganism having a mutation or deletion of a gene encoding CP1, and optionally having a mutation or deletion in at least one of the genes encoding apr, npr, epr, wpr, and mrp, or a method of producing a heterologous protein using a *Bacillus* or a *Bacilli* species of claim 14 having a mutation or deletion in a gene encoding CP1 and, optionally comprising a mutation or deletion in at least one of the genes encoding apr, npr, epr, wpr, and mrp.


WO 89/10976 teaches the inactivation of genes encoding *B. subtilis* cysteine and serine proteases in a neutral and alkaline protease-deficient *B. subtilis* host cell (abstract and pages 3, 4, 15, and 16) to create a mutant *B. subtilis* strain that is deficient in all four protease (cysteine, serine, alkaline, and neutral protease) activities (pages 15 and 16). WO 89/10976 teaches the use of the mutant cysteine, serine, alkaline, and neutral protease-null *B. subtilis* strain for heterologous expression of prolystaphin and lysostaphin, a metallopeptidase, using the mutant *B. subtilis* strain (pages 11, 12, 16, and 17). This anticipates claims 1, 4-9, and 13-17 as written.

Conclusion

14. No claim is in condition for allowance. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman


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